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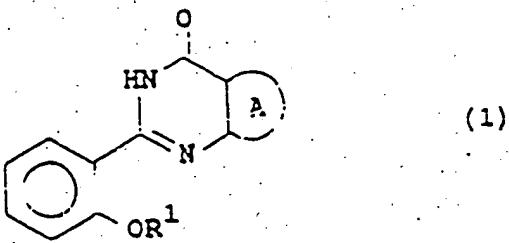
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⑫ Condensed pyrimidine derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

⑬ Compounds of the formula (1):

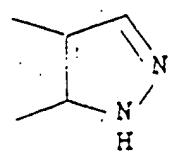


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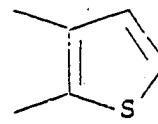
and pharmaceutically acceptable salts are described wherein



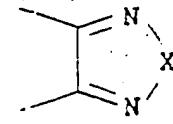
is a ring of sub-formula (a), (b) or (c):



(a)



(b)



(c),

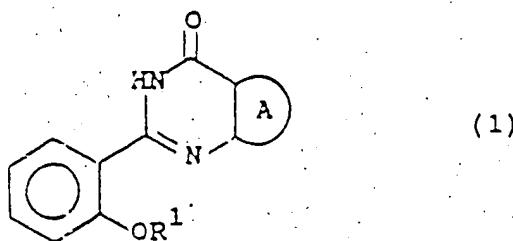
X is oxygen or sulphur, and

R' is C₁-alkyl, C₂-alkenyl, C₁-cycloalkylC₁-alkyl, or C₁-alkyl substituted by 1 to 6 fluoro groups.
Their use as medicaments, pharmaceutical compositions containing them and processes for their preparation are also described.

CHEMICAL COMPOUNDS

The present invention relates to fused pyrimidine derivatives, processes for their preparation, intermediates in their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combatting such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combatting chronic reversible obstructive lung diseases such as asthma and bronchitis. Furthermore the compounds of this invention are vasodilators and are therefore of value in combating angina, hypertension and congestive heart failure.

Accordingly the present invention provides compounds of the formula (1):

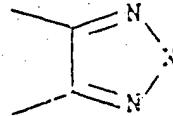
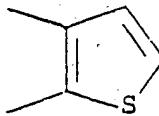
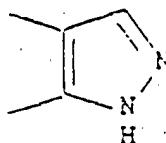


20 and pharmaceutically acceptable salts thereof, wherein



25

is a ring of sub-formula (a), (b) or (c):



35

(a)

(b)

(c),

40 X is oxygen or sulphur, and

R¹ is C₁-alkyl, C₂-alkenyl, C₃-cycloalkylC₁-alkyl, or C₁-alkyl substituted by 1 to 6 fluoro groups.

Suitably R¹ is C₂-alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R¹ is C₃-alkenyl for example allyl, butenyl or pentenyl.

Suitably R¹ is cyclopropylmethyl.

Examples of C₁-alkyl substituted by 1 to 6 fluoro groups include -CF₃, -CH₂CF₃ or -CF₂CHFCF₃.

Preferably R¹ is n-propyl.

Suitably



45

is group of sub-formula (a) thus forming a pyrazolo[3,4-d]pyrimidine ring system.

Suitably

(A)

5 is a group of sub-formula (b) thus forming a thieno[2,3-d]pyrimidine ring system.
Suitably

(A)

10 is a group of sub-formula (c) and X is oxygen thus forming a [1,2,5]oxadiazolo[3,4-d]pyrimidine ring system.
Suitably

15

(A)

20 is a group of sub-formula (c) and X is sulphur thus forming a [1,2,5]thiadiazolo[3,4-d]pyrimidine ring system.
Particular compounds of this invention are:
6-(2-propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one,
2-(2-propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one,
2-(2-propoxyphenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one
or pharmaceutically acceptable salts thereof.

This invention covers all tautomeric and optical isomeric forms of compounds of formula (1).
Compounds of the formula (1) may form pharmaceutically acceptable salts with
alkali metals for example sodium and potassium, or with an ammonium ion.
In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof
for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical
practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard

55 manner for the treatment of the indicated diseases, for example orally, sublingually, parenterally, trans-
dermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given
orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups,
tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution
40 of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or
colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used
for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose,
sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine
encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell.
45 Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely
used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses,
silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile
aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, or solubilising agent, for
50 example polyethylene glycol, polyvinylpyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil, or
sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically accept-
able salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for
example polymeric glycols, gelatins, coca-butter or low melting vegetable waxes or fats or their
synthetic analogues.

55 Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example
a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.
Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be

administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

5 Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

10 The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. The compositions of the present invention also have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, sublingually, topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

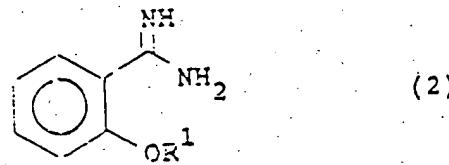
15 The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H₁-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-hypertensive agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil, diuretics such as thiazides and related compounds for example bendrofluazide, chlortalidone, chlorthalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

20 In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises:

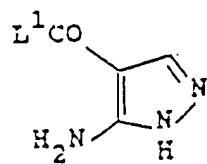
25 a) for compounds wherein

40 A

is a group of sub-formula (a), reacting a compound of the formula (2):



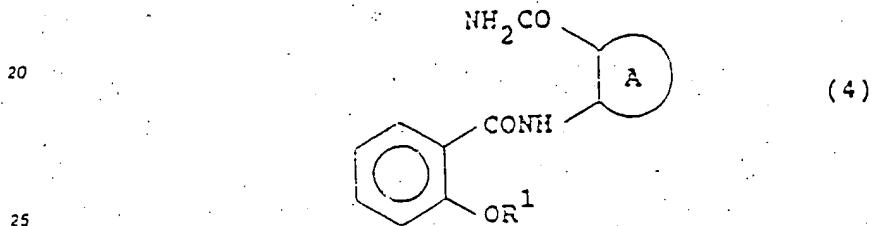
wherein R¹ is as hereinbefore defined with a compound of the formula (3):



10 wherein L^1 is C_1 -alkoxy or amino;
b) for compounds wherein



19 is a group of sub-formula (a) or (b), cyclising a compound of the formula (4) :



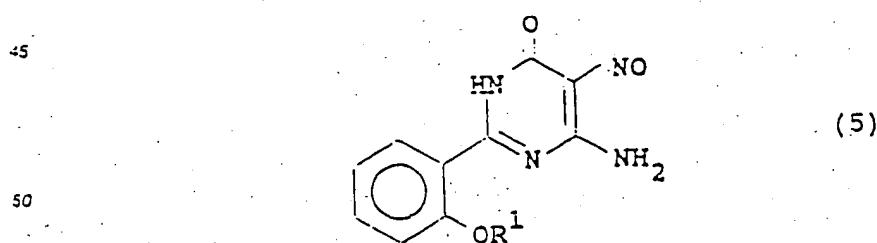
wherein R^1 is as hereinbefore defined and



35 is a group of sub-formula (a) or (b) as hereinbefore defined;
c) for compounds wherein

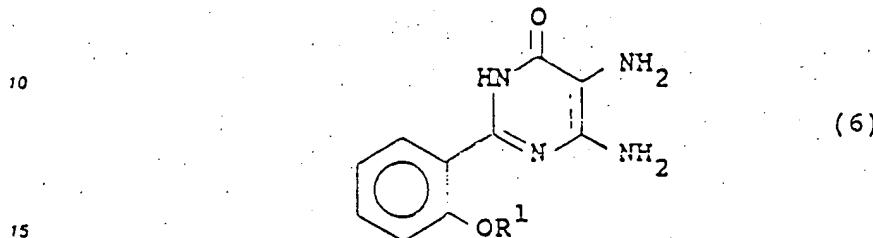


45 is a group of sub-formula (c) and X is oxygen, cyclising a compound of the formula (5) :



55 wherein R^1 is as hereinbefore defined with an oxidising agent;
d) for compounds wherein

5 is a group of sub-formula (c) and X is sulphur, reacting a compound of the formula (6):



of the base.

The following biological test method, data and Examples serve to illustrate this invention.

5. Bronchodilatation - *In vivo*

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methanoepoxy-PGH₂) was infused i.v. at a rate of 2.5 nmol/min. This produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The dose of compound required to reduce the U46619-induced bronchoconstriction by 50% is given as the ED₅₀. This result demonstrates *in vivo* anti-bronchoconstrictor activity.

15.

| Compound of Example | ED ₅₀ (μmol/kg) |
|---------------------|----------------------------|
| 1 | 5.13 |
| 2 | 2.62 |
| 4 | 4.51 |

25

Example 1

30. 6-(2-Propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one

A stirred mixture of 2-propoxybenzamidine methane-sulphonate (1.0 g), 3-amino-4-pyrazolecarboxamide sulphate (0.5 g) and sodium acetate (0.82 g) was heated in an oil bath (180 °C) for one hour. The reaction mixture was dissolved in hot 2 Normal sodium hydroxide (10 ml) and the solution was treated with charcoal and neutralised with glacial acetic acid. A precipitate was collected, washed with water and eluted from a silica column with chloroform. The combined fractions containing product were evaporated to dryness to afford the title compound, 148 mg, m.p. 182-183.5 °C.

40

Example 2

45. 2-(2-Propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one

a) A solution of 2-propoxybenzoyl chloride (0.99 g) in acetonitrile (7.5 ml) was added dropwise over 5 minutes to a cooled (0 °C), stirred mixture of 2-aminothiophene-3-carboxamide (0.71 g) and triethylamine (0.51 g) in acetonitrile (7.5 ml). The reaction mixture was stirred for one hour while being allowed to warm to ambient temperature and was then allowed to stand overnight. Acetonitrile was removed under reduced pressure and the residue was washed with water and recrystallised from ethanol-water to afford 2-(2-propoxybenzamido)thiophene-3-carboxamide, 0.91 g, m.p. 176.5-178.5 °C.

b) A stirred mixture of 2-(2-propoxybenzamido)thiophene-3-carboxamide (0.90 g) and pyridine (1 ml) in 2 Normal sodium hydroxide (25 ml) was heated under reflux for 2 hours. The cooled reaction mixture was neutralised with concentrated hydrochloric acid to afford a precipitate and the resulting mixture was extracted with chloroform (3 x 25 ml). The combined extracts were washed with water (20 ml) and brine (20 ml), dried (magnesium sulphate) and evaporated under reduced pressure to afford a crude product which was recrystallised from ethanol-water to afford the title compound, 0.41 g, m.p. 115-117 °C.

Example 3

5 2-(2-Propoxyphenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one

Lead tetraacetate (1 g) was added portionwise over 5 minutes to a stirred solution of 4-amino-5-nitroso-2-(2-propoxyphenyl)pyrimidin-6-one (0.52 g) in acetic acid (10 ml) under nitrogen. The reaction mixture was stirred for 1.5 hours and then allowed to stand overnight. A precipitate was collected, washed with water, dissolved in hot methanol and treated with charcoal. The methanolic solution was filtered through diatomaceous earth and the filtrate was evaporated under reduced pressure to afford a residue which was recrystallised from methanol to afford the title compound, 0.19 g, m.p. 163-164 °C.

15 Example 4

20 2-(2-Propoxyphenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one

A stirred solution of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one sulphate (0.72 g) in thionyl chloride (25 ml) was heated under reflux for 2 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue was washed with water and recrystallised from methanol-water and then from methanol to afford the title compound, 0.38 g, m.p. 157.5-158.5 °C.

25 Example 5

30 Pharmaceutical compositions for oral administration are prepared by combining the following:

| | % w/w | | | |
|----|---|-------|------|-------|
| 35 | 2-(2-Propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one | 0.5 | 3.0 | 7.14 |
| | 2% w/w Soya lecithin in soya bean oil | 30.45 | 68.2 | 64.41 |
| | Hydrogenated vegetable shortening and beeswax | 9.05 | 8.8 | 8.45 |

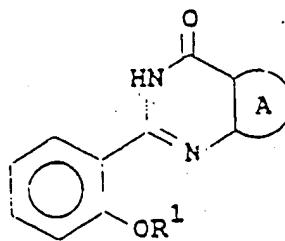
40 The formulations are then filled into individual soft gelatin capsules.

45 Example 6

A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 4 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

50 Claims

55 1. A compound of the formula (1):



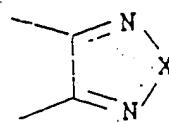
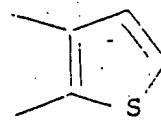
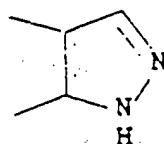
10 or a pharmaceutically acceptable salt thereof, wherein



15

is a ring of sub-formula (a), (b) or (c):

20



25

(a)

(b)

(c)

30 X is oxygen or sulphur, and
R¹ is C₁-alkyl, C₂-alkenyl, C₃-cycloalkylC₁-alkyl, or C₁-alkyl substituted by 1 to 6 fluor

2. A compound according to claim 1 wherein R¹ is C₂-alkenyl.
3. A compound according to claim 1 wherein R¹ is n-propyl.
4. A compound according to any one of claims 1 to 3 where

35



40 is a group of sub-formula (a).

5. A compound according to any one of claims 1 to 3 where



45

is a group of sub-formula (b).

6. A compound according to any one of claims 1 to 3 where

50



55 is a group of sub-formula (c) and X is oxygen.

7. A compound according to any one of claims 1 to 3 where

(A)

is a group of sub-formula (c) and X is sulphur.

8. A compound according to claim 1 which is :

6-(2-propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one,
2-(2-propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8 for use as a medicament.

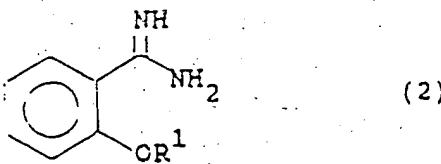
10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

11. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises :

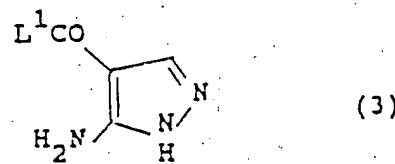
a) for compounds wherein

(A)

25 is a group of sub-formula (a), reacting a compound of the formula (2):



35 wherein R¹ is as defined in claim 1 with a compound of the formula (3) :



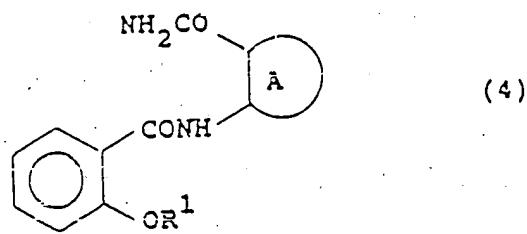
45 wherein L¹ is C₁-alkoxy or amino;

b) for compounds wherein

(A)

50 is a group of sub-formula (a) or (b), cyclising a compound of the formula (4) :

55



10 wherein R¹ is as hereinbefore defined and



15

is a group of sub-formula (a) or (b) as defined in claim 1;

c) for compounds wherein

20

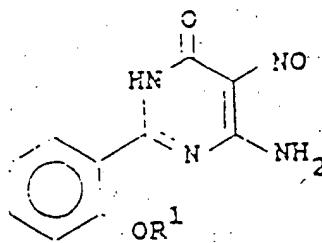


25

is a group of sub-formula (c) and X is oxygen, cyclising a compound of the formula (5):

30

(5)



35

wherein R¹ is as hereinbefore defined with an oxidising agent;

d) for compounds wherein



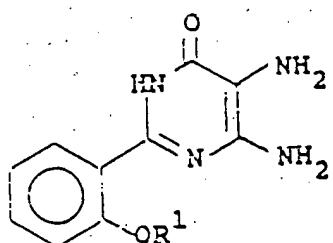
45

is a group of sub-formula (c) and X is sulphur, reacting a compound of the formula (6):

50

(6)

55

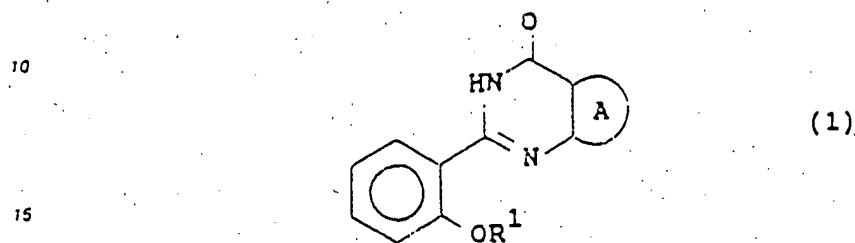


wherein R' is as hereinbefore defined with trialkyl chloride or a chemical equivalent thereof; and thereafter optionally forming a pharmaceutically acceptable salt.

12. A compound of the formula (4) as defined in claim 11.

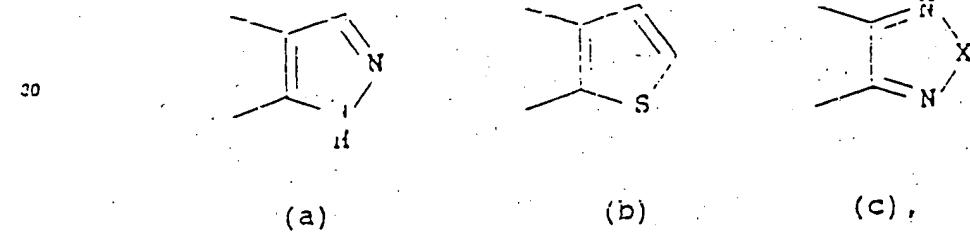
5 Claims for the following Contracting State: ES

1. A process for preparing a compound of the formula (1) :



20 or a pharmaceutically acceptable salt thereof, wherein:

25 is a ring of sub-formula (a), (b) or (c):

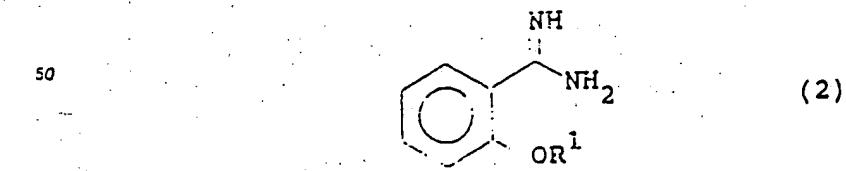


35 X is oxygen or sulphur, and
R' is C₁-alkyl, C₂-alkenyl, C₃-cycloalkylC₁-alkyl, or C₁-alkyl substituted by 1 to 6 fluoro groups,
which process comprises:

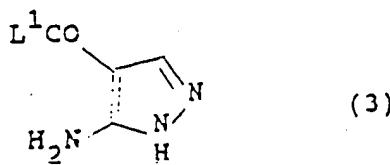
40 a) for compounds wherein



is a group of sub-formula (a), reacting a compound of the formula (2):



55 wherein R' is as hereinbefore defined with a compound of the formula (3) :

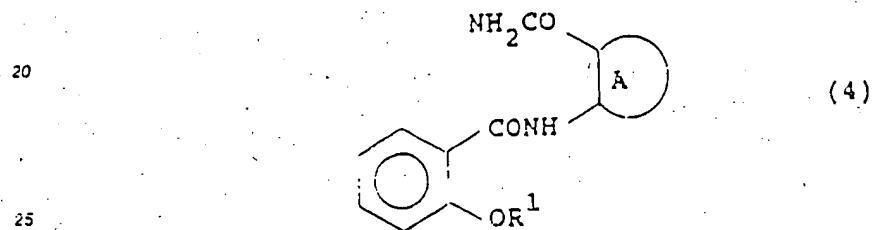


wherein L^1 is $\text{C}_1\text{-alkoxy}$ or amino;
 10. b) for compounds wherein



15

is a group of sub-formula (a) or (b), cyclising a compound of the formula (4):



wherein R^1 is as hereinbefore defined and

30

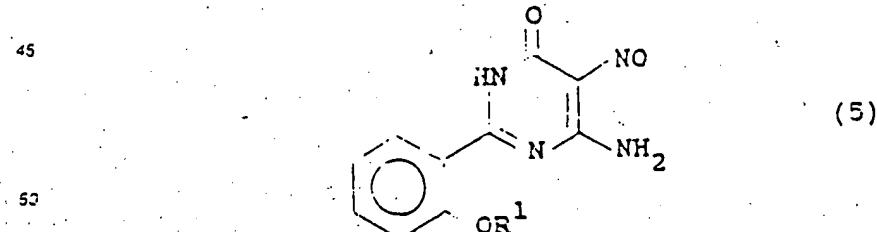


35 is a group of sub-formula (a) or (b) as defined in claim 1;
 c) for compounds wherein

40



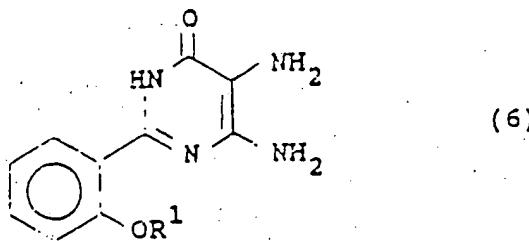
is a group of sub-formula (c) and X is oxygen, cyclising a compound of the formula (5):



55 wherein R^1 is as hereinbefore defined with an oxidising agent;
 d) for compounds wherein

5 is a group of sub-formula (c) and X is sulphur, reacting a compound of the formula (6) :

10



15

(6)

wherein R¹ is as hereinbefore defined with thionyl chloride or a chemical equivalent thereof; and thereafter optionally forming a pharmaceutically acceptable salt.

20 2. A process according to claim 1 for preparing a compound wherein R¹ is C₂-alkyl.
3. A process according to claim 1 for preparing a compound wherein R¹ is n-propyl.
4. A process according to any one of claims 1 to 3 for preparing a compound wherein

25

A

is a group of sub-formula (a).

30 5. A process according to any one of claims 1 to 3 for preparing a compound wherein

35

A

is a group of sub-formula (b).

6. A process according to any one of claims 1 to 3 for preparing a compound wherein

40

A

is a group of sub-formula (c) and X is oxygen.

45 7. A process according to any one of claims 1 to 3 for preparing a compound wherein

50

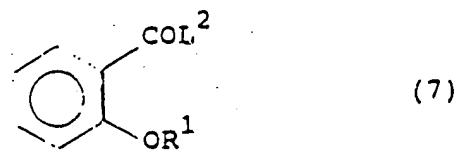
A

is a group of sub-formula (c) and X is sulphur.

8. A process according to claim 1 for preparing a compound which is :
6-(2-propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one,
2-(2-propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one,
55 2-(2-propoxyphenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.
9. A process for preparing a pharmaceutical composition which comprises bringing into association a

compound of the formula (1) as defined in any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

10 10. A process for preparing a compound of the formula (4) as defined in claim 1 which comprises reacting 3-amino-4-pyrazolocarboxamide or 2-aminothiophene-3-carboxamide with a compound of the formula (7):

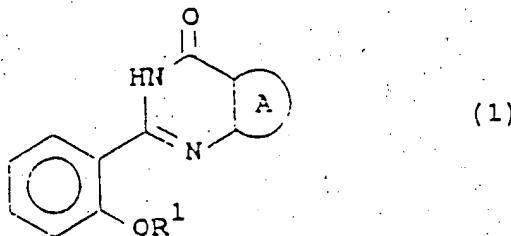


15 wherein R¹ is as defined in claim 1 and L² is halo.

15 Claims for the following Contracting State : GR

1. A process for preparing a compound of the formula (1) :

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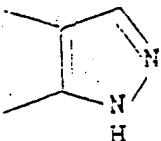
30 or a pharmaceutically acceptable salt thereof, wherein



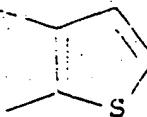
35

is a ring of sub-formula (a), (b) or (c):

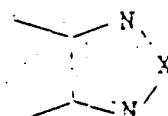
40



(a)



(b)



(c),

45

50 X is oxygen or sulphur, and R¹ is C₁-alkyl, C₂-alkenyl, C₃-cycloalkylC₁-alkyl, or C₁-alkyl substituted by 1 to 6 fluoro groups.

55 which process comprises:

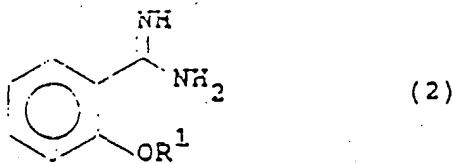
a) for compounds wherein

55



is a group of sub-formula (a), reacting a compound of the formula (2):

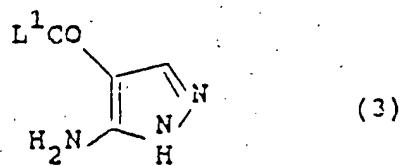
5



wherein R^1 is as hereinbefore defined with a compound of the formula (3) :

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wherein L^1 is $\text{C}_1\text{-alkoxy}$ or amino;

b) for compounds wherein

20

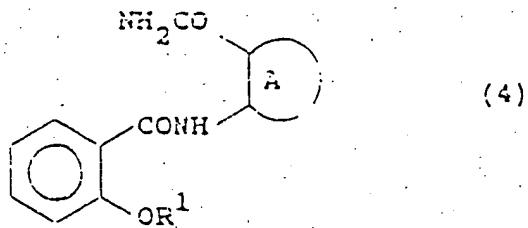


25

is a group of sub-formula (a) or (b), cyclising a compound of the formula (4) :

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wherein R^1 is as hereinbefore defined and

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is a group of sub-formula (a) or (b) as defined in claim 1;

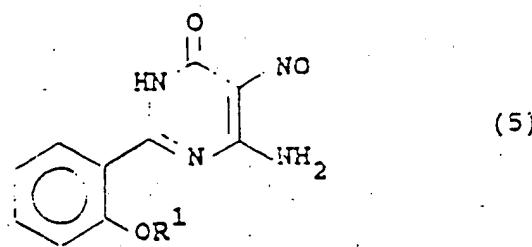
c) for compounds wherein

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is a group of sub-formula (c) and X is oxygen, cyclising a compound of the formula (5) :

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5



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wherein R¹ is as hereinbefore defined with an oxidising agent;
d) for compounds wherein

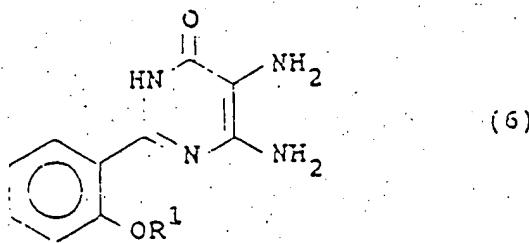
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20

is a group of sub-formula (c) and X is sulphur, reacting a compound of the formula (6):

25



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wherein R¹ is as hereinbefore defined with thionyl chloride or a chemical equivalent thereof;
and thereafter optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound wherein R¹ is C₂-alkyl.

3. A process according to claim 1 for preparing a compound wherein R¹ is n-propyl.

4. A process according to any one of claims 1 to 3 for preparing a compound wherein

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is a group of sub-formula (a).

5. A process according to any one of claims 1 to 3 for preparing a compound wherein.

45



50 is a group of sub-formula (b).

6. A process according to any one of claims 1 to 3 for preparing a compound wherein

55



is a group of sub-formula (c) and X is oxygen.

7. A process according to any one of claims 1 to 3 for preparing a compound wherein

5 is a group of sub-formula (c) and X is sulphur.

8. A process according to claim 1 for preparing a compound which is :

6-(2-propoxypyhenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one,

2-(2-propoxypyhenyl)thiено[2,3-d]pyrimidin-4(3H)-one, or

10 2-(2-propoxypyhenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one, or

2-(2-propoxypyhenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one,

or a pharmaceutically acceptable salt thereof.

9. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (1) as defined in any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

15 10. A compound of the formula (4) as defined in claim 1.

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